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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,993	CHANG ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 7-26* is/are pending in the application.

4a) Of the above claim(s) *16-17, 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7-15,18-21,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on August 6, 2007, has been received and entered. Claims 2-3, 6, 14, 27-66 have been canceled, while applicants have amended claims 1 and 4.

This action is non-Final.

Claims 1, 4-5, 7-25 and 26 are pending.

Election/Restrictions

Applicant's election with traverse of the invention of claims 1-26 (group I) filed September 18, 2006 was acknowledged. It was noted that applicants elected 2D-CD4 as species for examination in a supplementary response filed on 12/28/2006. It is noted that claims 16-17, 22-24 do not read on elected species and therefore claims 16-17, 22-24 were also withdrawn. Claims 16-17, 22-24 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 18, 2006.

The requirement is still deemed proper and was therefore made FINAL.

Claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are under examination.

Withdrawn-Claim Objections

The objection to claims 7-10 for not complying with the sequence rules is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1, 4-5, 7-15, 18-21, 25 and 26 rejected under 35 U.S.C. 112, first paragraph is withdrawn in view of amendments to the claims. Examiner would

agree that as amended instant claims are fully enabled. However, upon further consideration a new rejection is presented below.

New Grounds of Claim Rejections - 35 USC § 112

Claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated Lactobacillus jensenii bacterium comprising an expression cassette, the expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and a biologically-active polypeptide, wherein the biologically active polypeptide is linked to a heterologous carboxyl terminal cell wall targeting region and wherein the cell wall targeting region comprises SEQ ID NO:7 or SEQ ID NO:8 or variants thereof in which LPQTG (SEQ ID NO:13) in SEQ ID NO:7 or SEQ ID NO:8 is replaced with LPQSG (SEQ ID NO:I 1), LPQAG (SEQ ID NO:12), or LPQTA (SEQ ID NO:14), wherein the biologically active polypeptide is expressed in the cell wall of the bacterium, does not reasonably provide enablement for a non-isolated *Lactobacillus jensenii* comprising expression cassette. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in *In re Wands*, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction

and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

It is noted that instant claims are directed to a composition, however, they have been analyzed for *Lactobacillus jensenii* that is transformed under *in vivo* condition.

The claimed invention is directed to a genetically modified *Lactobacillus jensenii* that is vagina-colonizing strain comprising an exogenous gene encoding the biologically active protein. It is noted that dependent claims limit the cell wall targeting region comprising plurality of anchoring sequences. Claims 15, 18-21 limit the biologically active protein that binds to pathogen when contacted with the pathogen subsequently limiting to HIV pathogen. Claims 20 and 21 limit the biologically active protein to include CD4 subsequently limiting to include 2D-CD4.

As recited it is not apparent whether breadth of the claim embraces *Lactobacillus jensenii* that is isolated or the any *Lactobacillus jensenii* including one naturally occurring bacterium that is transfected with the expression cassette of the invention under *in vivo* condition. It is noted that recitation of "an isolated *Lactobacillus jensenii* " would obviate the basis of the rejection.

The instant specification and the prior art provide sufficient guidance to indicate that surface expression of proteins via covalent linkage with peptidoglycans in Gram-positive bacteria involves unique sorting signals and sortase-dependent machinery. The prior art also teaches plurality of genetically modified bacterium for

the expression of biologically active protein (see US patent 6,190,662, dated 2/20/2001 and WO 96/11277, art of record). The specification teaches that the all the three cell wall anchored proteins identified after genomic sequencing of *L. jensenii* 1153 have LPQTG sorting signal preceding a hydrophobic region and a charged C-terminal tail and possess unique long repetitive sequences (see figure 1 of the specification). In addition, instant specification has exemplified a stretch of 95 amino acids containing one tandem repeat in fusion with the C-terminal cell wall sorting signal in pOSEL268 (Examples and see Figure 7) enables surface display of CD4 in *Lactobacillus jensenii.* The specification provides guidance with respect to an isolated *Lactobacillus jensenii* (emphasis added) comprising an expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and a biologically active polypeptide, wherein the biologically active polypeptide is 2CD4 linked to a heterologous carboxyl terminal cell wall targeting region. However, it does not provide specific information required by the Artisan to reasonably predict a *Lactobacillus jensenii* comprising any biologically active protein inserted into the cell wall will express the protein at the surface intended to treat variety of condition.

Claims 1, 4-5, 7-12, 18-21, 25 and 26 embrace a genetically modified *Lactobacillus jensenii* that is intended for the treatment of variety of viral infections. The specification contemplates biologically active protein refers to any amino acid sequence that has the biological activity of the amino acid sequence within, or outside of, a native cell (see para 35 of the published application). In addition, specification contemplates polypeptides of the invention can be of any size and molecular weight (See para. 112). The specification has exemplified *Lactobacillus jensenii* expressing 2-CD4 on the surface (see example and para 115 of the published application). In the instant case, as recited instant claims do not even require expression of any protein rather it merely requires presence of expression cassette. It is apparent from the cited arts that biological function of a protein,

peptide or its fragments were unpredictable at the time of the invention and even same short stretch of amino acid sequence could show diverse biological functions while surrounded by different background amino acid sequences. Prior to instant invention, Davis, (New Biologist, 1990, 2(5), 410-419, art of record) teaches that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid. The applicant's disclosure does not enable one skilled in the art to practice the invention commensurate with full scope without further undue amount of experimentation, which requires the expression of protein at the surface of the isolated *Lactobacillus jensenii* at a level such that it shows contemplated biological activity. Absent of evidence to the contrary, it is not clear that whether any biologically active protein of any size would be functional could be expressed in same manner as they have been demonstrated for 2D-CD4, particularly since claims 1, 4-5, 7-12, 18-21, 25 and 26 do not require expression of the protein. An artisan would have to perform undue experimentation to empirically test by trial and error different nucleic acid encoding protein to practice the *L. jensenii* comprising diverse group of biologically active protein such that it is expressed at the surface intended for the treatment of variety of disease to make use of the invention without reasonable expectation of success.

Claims also embrace *Lactobacillus jensenii* that is isolated and any naturally occurring bacterium that is transfected with the expression cassette of the invention under *in vivo* condition. The guidance in the specification is limited to an isolated *Lactobacillus jensenii* comprising expression cassette expressing nucleic acid encoding a biologically active protein that binds to a pathogen when it is contacted with the pathogen. The specification does not provide any guidance with

respect to transforming *Lactobacillus jensenii* under *in vivo* condition. In a post filing art Chang et al (Proc Natl Acad Sci U S A. 2003; 100(20): 11672–11677) discloses 2D CD4 produced by these bacteria exhibit full biological activity *in vitro*, defined by the ability to bind gp120 and to inhibit HIV-1 viral entry. There is no evidence on record that genetically modified *Lactobacillus jensenii* would be efficacious in vivo in same mummer as exemplified for in vitro condition. An artisan of skill would have to perform undue experimentation to make and use the composition as claimed because the art of expressing any protein from genetically modified bacterium using any heterologous carboxy terminal cell wall targeting region intended for the treatment of condition under in vivo condition was not predictable as supported by the art of record.

In conclusion, in view of breadth of the claims and absence of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions commensurate with full scope of the claim. The specification and prior art enables "an isolated Lactobacillus jensenii bacterium comprising an expression cassette, the expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and a biologically-active polypeptide, wherein the biologically active polypeptide is linked to a heterologous carboxyl terminal cell wall targeting region and wherein the cell wall targeting region comprises SEQ ID NO:7 or SEQ ID NO:8 or variants thereof in which LPQTG (SEQ ID NO:13) in SEQ ID NO:7 or SEQ ID NO:8 is replaced with LPQSG (SEQ ID NO:I 1), LPQAG (SEQ ID NO:12), or LPQTA (SEQ ID NO:14), wherein the biologically active polypeptide is expressed in the cell wall of the bacterium.

Withdrawn-Claim Rejections - 35 USC § 112-Written Description

Claims 1, 4-5, 7-15, 18-21, 25 and 26 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1-5, 7-15, 18-21 and 25-26 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims are vague and indefinite to the extent metes and bounds of these claims are unclear. It is not apparent whether *Lactobacillus jensenii* is isolated or it is any naturally occurring bacterium *Lactobacillus jensenii* that is transfected with the expression cassette of the invention under *in vivo* condition. Recitation of "an isolated *Lactobacillus jensenii* " would obviate the basis of the rejection. Claims 4-5, 7-13, 15, 18-21, 25 and 26 directly or indirectly depend on claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4-5, 13-14 and 25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Tagliabue et al (WO 96/11277, IDS, art of record) as evidenced by Steidler et al (US patent 6,190,662, dated 2/20/2001).

The claims embrace *Lactobacillus jensenii* comprising a sequence that encodes a heterologous protein comprising a promoter operably linked to a polynucleotide encoding a biologically active polypeptide linked to a cell wall targeting region comprising cell wall associated sequence, LPQ(S/A/T)(G/A) and hydrophobic sequence. Independent claims do not require biologically active polypeptide to be expressed in the cell wall of the bacterium.

Tagliabue et al that teach plurality of recombinant bacterium including *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. It is noted that Tagliabue et al contemplated recombinant *Lactobacillus* including *Lactobacillus jensenii* and *L. Lactis* (see Tagliabue et al, pages 8-10, especially page 10, line 25). In addition, prior art as evidenced by Steidler et al teach a method to transform Gram-positive host organism with a recombinant vector. Steidler et al disclose a recombinant *Lactococcus lactis* comprising a chimeric gene containing nucleic acid encoding a secretion signal sequence, a desired protein or polypeptide and a cell wall attachment domain, such

as that derived from *Staphylococcus aureus* protein A of the LPXTG motif. It is noted that Steidler contemplated cell wall anchoring domain comprises, at the C-terminal, anchoring domain derived from the *Staphylococcus aureus* protein A, however, other proteins could also be used as the cell wall anchoring domain. Thus, it is clear that Seidler contemplate any heterologous anchoring domain as long as they have properties of being stably bound to the surface of the cell and are capable of representing the desired protein on the cell surface. Since claim embrace cell wall targeting region comprises SEQ ID NO: 7 or 8 or variant thereof. Thus, disclosure of Tagliabue et al directed to genetically modified *Lactobacillus jensenii* would embrace the entire necessary element known in the art to express protein and as evidenced from the teaching of Seidler. It is emphasized that different anchor cell wall sorting signal sequences are inherently present in gram-positive bacterium including *Lactobacillus jensenii.* Thus, recombinant *Lactobacillus jensenii* disclosed by Tagliabue et al and those embraced by the instant claims appear to be structurally same. See MPEP 2131.02, which recites when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).* Tagliabue teaches recombinant *Lactobacillus jensenii* for treating a virus in an animal (see page 18). Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the

characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, Tagliabue et al (WO 96/11277) anticipate claims 1, 4-5, 13-14 and 25-26.

Claims 1, 4-5, 7-15, 18-21, 25 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Chang et al (US 7179,458, dated 2/20/2007, effective filing date 3/8/2002) or Chang et al (US patent application number US 2007/0117197, dated 5/24/2007, effective filing date 3/8/2002).

The applied references have common inventors and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims embrace *Lactobacillus jensenii* comprising a sequence that encodes a heterologous protein comprising a promoter operably linked to a polynucleotide encoding a biologically active polypeptide linked to a cell wall targeting region comprising cell wall associated sequence comprising SEQ ID NO: 7 or 8 or its variant containing LPQ(S/A/T)(G/A) and hydrophobic sequence. It is noted that independent claims do not require biologically active polypeptide to be expressed in the cell wall of the bacterium.

Chang et al teach *Lactobacillus jensenii* comprising a sequence that encodes a heterologous protein comprising a promoter operably linked to a polynucleotide encoding a biologically active polypeptide linked to a cell wall targeting region. It is noted that Chang et al also disclose a method of making and administering recombinant bacterium. Chang et al also disclose that the recombinant

Lactobacillus jensenii expresses CV-N protein HIV inhibitory protein. The secreted CV-N protein disclosed by Chang et al would inherently posses amino acid of mature *Lactobacillus jensenii* protein because of cleavage within the signal sequence. Thus, disclosure of Chang et al directed to genetically modified *Lactobacillus jensenii* would embrace necessary element known in the art to express protein.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1-5, 13-14 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277, IDS), Steidler et al (US patent 6,190,662, dated 2/20/2001), Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001). Applicant's arguments with respect to instant claims have been considered but are moot in view of the new grounds of rejection.

Claims 1-5, 7-10, 13-14 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277), Steidler et al (US patent 6,190,662, dated 2/20/2001), Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001) and Navarre et al (Microbiol Mol Biol Rev. 1999; 63(1): 174-229, IDS). Applicant's arguments with respect to instant claims have been considered but are moot in view of the new grounds of rejection.

Claims 1-5, 7-10, 13-15, 18-21 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277), Steidler et al (US patent 6,190,662, dated 2/20/2001); Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001) Boyd (US 6,193,982, IDS) and Vallor et al. (The Journal of Infectious Diseases, 184:1431-6,

2001, IDS). Applicant's arguments with respect to instant claims have been considered but are moot in view of the new grounds of rejection.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-5, 7-15, 18, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277), Steidler et al (US patent 6,190,662, dated 2/20/2001, art of record), Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001, art of record) and Navarre et al (Microbiol Mol Biol Rev. 1999; 63(1): 174-229, IDS).

The claims embrace *Lactobacillus jensenii* comprising a sequence that encodes a heterologous protein comprising a promoter operably linked to a polynucleotide encoding a biologically active polypeptide linked to a cell wall targeting region comprising cell wall associated sequence, LPQ(S/A/T)(G/A) and hydrophobic sequence. It is noted that independent claims do not require biologically active polypeptide to be expressed in the cell wall of the bacterium.

Tagliabue et al that teaches plurality of recombinant bacterium including *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. It is noted that Tagliabue et al contemplated recombinant *Lactobacillus* including *Lactobacillus jensenii* and *L. Lactis* (see Tagliabue et al,

pages 8-10, especially page 10, line 25). Thus, it is clear that LPQTG anchor cell wall sorting signal sequences are inherently present in gram-positive bacterium including *Lactobacillus jensenii.* However, Tagliabue differed from claimed invention by not disclosing other signal sequence for expression of protein.

Steidler et al teach Gram-positive host organism transformed with a recombinant vector, such as *Lactococcus lactis* comprising a chimeric gene containing nucleic acid encoding a secretion signal sequence, a desired protein or polypeptide and a cell wall attachment domain, such as that derived from *Staphylococcus aureus* protein A of the LPXTG motif (see col. 2, lines 46-53). It is noted that Steidler contemplated cell wall anchoring domain comprises, at the C-terminal, anchoring domain derived from the *Staphylococcus aureus* protein A, however, other proteins could also be used as the cell wall anchoring domain. Thus, it is clear that Seidler contemplate any heterologous anchoring domain as long as they have properties of being stably bound to the surface of the cell and are capable of representing the desired protein on the cell surface. Steidler also teach that the Gram-positive host organism of *Lactococcus* host would express desired protein and are covalently attached to the cell wall and is displayed on the outer face of the surface of the host organism (see entire col. 2). It is noted that Seidler et al also disclose that nucleic acid encoding the fusion protein is operably linked to control sequences to direct its expression (see col. 4, 22-32). Seidler taught a Gram-positive host more specifically *Lactococcus lactis* bacterium comprising the entire claimed element, but Seidler differed from claimed invention by not teaching *Lactobacillus jensenii.*

Schneewind teach different motifs that can be employed in expressing a polypeptide of interest on the surface of bacteria that are recognized by Srt A or Srt B (See para. 11 of the publication) including LPQTG EESNKDMTLPLMALLAL SSIVAFVLP RKRKN SEQ ID NO. 25 (see table 1 and para 54). Schneewind contemplated that the sorting signal may include all or part of the sequences

NPQ/KTN/G or LPX3X4G, where X3 is any of the 20 naturally occurring amino acid and X is an alanine, serine, or threonine (see para. 166 of the published application). It is noted that Schneewind generally embraced the idea of a polypeptide with a sorting signal with a LPX3X4G motif that may further include hydrophobic domain of at least 31 amino acids carboxyl to the motif and a charged tail region (see para. 20), he did not teach a genetically modified *Lactobacillus jensenii* expressing any polypeptide.

Prior to instant invention, art teaches that most cell wall anchored proteins from Gram-positive bacteria share the same sorting signal LPXTG, some of the proteins, however, have different motifs. Navarre et al disclose that the LPXTG motif is conserved within the sorting signals of all known wall-anchored surface proteins of gram-positive bacteria (see Table 1). It is noted that Navarre teach that threonine (T) displays some variation in that either alanine or serine can be found at this position. In addition, Navarre discloses a threonine-to-alanine substitution in the sorting signal of staphylococcal protein A and resulting mutation showing no affect in anchoring suggesting that these sequences could be functional sorting signals. In addition, Navarre also discloses other mutations such as a proline (P)-to-asparagine (N) mutation, resulting in abolishment of sorting signal. These suggest that proline being the critical element and cannot be substituted with any other amino acid residue (see page 184, col. 1, para. 2). However, Navarre et al differed from claimed invention by not disclosing genetically modified *Lactobacillus jensenii.*

Accordingly, in view of the teachings of Tagliabue et al, Schneewind, Steidler and Navarre, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the recombinant *Lactobacillus jensenii* disclosed by Tagliabue to include expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and biologically active polypeptide that is anchored to a cell wall targeting region comprising different signal sequence as disclose by Navarre and Schneewind with

a reasonable expectation of success. It is noted that Schneewind and Navarre taught that gram-positive bacteria sorting signal LPXTG is mostly conserved but some have different motifs. Given that different genome, sequencing and homology searches of different strains of gram-positive bacteria including *Lactobacillus jensenii* were available and routine to one of ordinary skill in the art. It would have been prima facie obvious to one of ordinary skill in the art to use other motifs such as LPQTG to express polypeptide of interest on the surface of bacteria as per the teachings of Schneewind. In addition, Navarre disclosed importance of other amino acid at different positions in optimizing protein expression and also indicated the necessity proline (P) (supra), which cannot be substituted with any other amino acid residue. It would have obvious for a person of ordinary skill in the art to try LPQTG as cell wall anchor sequence as disclosed by Schneewind on the basis with other elements disclosed by Steidler to create genetically modified *L. jensenii* as disclosed in the instant application with predictable results.

One who would practiced the invention would have had reasonable expectation of success because Tagliabue et al had already described *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. Schneewind and Steidler and Navarre provide necessary elements and guidance to express protein on other Gram-positive bacterium using different cell wall associated sequence to optimize the protein expression as per the teaching of Navarre.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277, art of record), Steidler et al (US patent 6,190,662, dated 2/20/2001, art of record); Schneewind et al (US

patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001, art of record) Boyd (US 6,193,982, IDS) and Vallor et al. (The Journal of Infectious Diseases, 184:1431-6, 2001, IDS).

The combined teaching Tagliabue et al, Schneewind and Steidler have been discussed above and relied in same manner here. However, none of the references teach a genetically engineered *Lactobacillus jensenii* comprising a nucleotide sequence encoding CD4 or an HIV-binding fragment of CD4, wherein CD4 or an HIV-binding fragment of CD4 bind to HIV.

However, at the time the invention was made, Boyd teaches that cyanovirin-N, which binds to gp120 of immunodeficiency virus, can be used treat viral infections (columns 4, 6-7, and 15). Cyanovirin-N is an 11kDa protein. Boyd teaches that exploiting the HIV gp120-targeting properties of sCD4 (also known as two-domain soluble CD4 protein) was known to one of ordinary skill in the art (column 10). In addition, Boyd teaches that it is well established that lactobacilli can be readily transformed using available genetic engineering techniques (column 15). Boyd teaches that lactobacilli can be used as the delivery vehicle for a cyanovirin (columns 6-7 and 15-18). Boyd teaches that lactobacilli has been used against pathogenic bacterial or yeast infections of the urogenital tract based on the endogenous production of virucidal levels of H_2O_2 and/or lactic acid and/or other potentially virucidal substances (column 16). Boyd teaches that lactobacilli are prominent, nonpathogenic inhabitants of other body cavities (column 15). However, Boyd does not specifically teach using modifying *Lactobacillus jensenii*.

Vallor et al. teach that *Lactobacillus jensenii* produces H_2O_2 and is predominant lactobacilli in the vagina (page 1431).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Tagliabue et al, Schneewind and Steidler taken with Boyd and Vallor, to produce a genetically

engineered *Lactobacillus jensenii* expressing a nucleotide sequence encoding a virus binding fragment to the vagina of a mammal. One of ordinary skill in the art would have been motivated to use *L. jensenii* as the recombinant bacterium for delivering a biologically active protein to the vagina of a mammal because *L. jensenii* is reported to colonize in the vagina as disclosed by Vallor (page 1431). In addition, one of ordinary skill in the art would have been motivated to combine the teaching to delivery a nucleotide sequence a viral binding fragment of cyanovirin-N using genetically engineered *Lactobacillus jensenii* to a mammalian mucosal surface cell in vitro to study the binding of cyanovirin-N to a viral pathogen as taught by Boyd (column 39). In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Tagliabue et al, Schneewind and Steidler taken with Boyd and Vallor, to produce a genetically engineered *Lactobacillus jensenii* a nucleotide sequence encoding a two domain soluble CD4 (2D-CD4). One of ordinary skill in the art would have been motivated to combine the teaching to delivery a nucleotide sequence encoding 2D-CD4 using genetically engineered *Lactobacillus jensenii* to a mammalian's mucosal cells in vitro to study the binding of 2D-CD4 to a viral pathogen as taught by Boyd (columns 15-17 and 39). In view of the teaching of Tagliabue and Boyd and the teaching in the specification, one of ordinary skill in the art would have a reasonable expectation of success for producing the claimed *Lactobacillus jensenii.*

Therefore, the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not

patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/620,588. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a *Lactobacillus jensenii* bacterium recombinantly altered to express any biologically active protein when it is contacted with a pathogen. It is noted that claims of '588 claims differ only with respect to a broader scope of biologically active protein and specific elements to recombinantly alter bacterium set forth in claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 that are broadly encompassed those specifically claimed in claims 1-12 of '588. Therefore, the claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 of the instant application are embraced by claims 1-12 of co-pending application '588.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of copending Application No. 11/331,965. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a *Lactobacillus jensenii* bacterium recombinantly altered to express any biologically active protein when it is contacted with a pathogen. It is noted that claims of '965 claims differ only with respect to a broader scope of biologically active protein and specific elements to recombinantly alter bacterium set forth ion claims 1, 4-5, 7-13, 15, 18-21, 25 and 26 are broadly encompassed those specifically claimed in claims 1-2 of '965. Therefore, the claims 1-5, 7-15, 18-21, and 25-26 of the instant application are encompassed by claims 1-2 of co-pending application '965.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Pallen et al . An embarrassment of sortases - a richness of substrates? Trends Microbiol. 2001, 9(3):97-102, IDS).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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